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GlaxoSmithKline

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Management Dockets, N/A
Dockets Management Branch
Food and Drug Administration
HFA-305
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Re: Docket 2005D-0047
Draft Guidance for Industry: Considerations for Plasmid Deoxyribonucleic Acid Vaccines for Infectious Disease Indications

Dear Madam or Sir:

Enclosed please find comments from GlaxoSmithKline, including general and specific comments for the Draft Guidance for Industry: Considerations for Plasmid Deoxyribonucleic Acid Vaccines for Infectious Disease Indications. These comments are presented for consideration by the FDA. The general comments are presented first, with the specific comments presented in order by section in the draft guidance.

GlaxoSmithKline appreciates the opportunity to provide feedback and suggestions for this draft guidance. I am submitting the comments for this draft guidance by hardcopy. Therefore, you will receive this letter with two copies of comments.

If you have any questions about these provided comments, please do not hesitate to contact me at (919) 483-5857. Thank you for your consideration.

Sincerely,

Mary Faye S. Whisler, Ph.D.
Assistant Director
New Submissions, North America

2005D-0047

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General Comments:
As a general observation this guidance has been written with administration of DNA solutions in mind and some of the issues may not be relevant to other types of formulation and/or routes of administration.

Specific Comments:

Section/Paragraph/Line	Original Text	Comments
Section II A/Paragraph 2/ Last line	"..and that you establish the genetic stability of the MCB and WCB"	Clarification is requested on whether establishing the genetic stability is a discrete work package conducted as MCB characterisation or an ongoing commitment to monitor the stability of MCB and WCB for as long as they are in use. Genetic stability is also part of the work performed to determine the limit of *in vitro* cell age whereby cells from the MCB or WCB are compared with cells at *ivca* limit as part of process validation.
Section II B/Paragraph 1/ Line 5	"We recommend that you evaluate bulk plasmid preparations for the presence of bacterial host cell contaminants to include DNA, RNA, and protein and set limits for the maximum level of each of these contaminants. We generally recommend that host cell contaminants be at as low a concentration as is technically feasible"	The term "as low a concentration as is technically feasible" is not helpful as it may be technically, but not logistically, feasible to reduce levels to unnecessarily low levels, given the low dose and route of administration of some DNA vaccine products. In recent interactions with other sponsors, CBER has required that host cell DNA, RNA and protein contaminant concentration each be <1%. Clarification of the acceptable level is needed in this guidance. Residual bacterial gDNA does not have the same safety issues associated with it as mammalian DNA. However, it is acknowledged that manufacturers should be working towards what is technically feasible and justifiable based on a thorough assessment of the risks. Clarification is needed for the level of this specific gDNA. Additionally, clarification is needed as to the type of HCP assay required.
Section II B/Paragraph 2/ Line 12	"....bacterial endotoxins and endotoxin contamination should not exceed 5.0 EU/kg body weight for the intended recipients"	The proposed wording is consistent with pharmacopoeial standards for drug products but not bulk drug substance. It may be more helpful to state that the maximum EU limits per kg of body weight should be applied to the drug product, and that this be based on dose and route of administration.

(Continued)

Specific Comments (Continued):

Section/Paragraph/Line	Original Text	Comments
Section II B/Paragraph 4/ Line 6	"....you provide evidence that *in vitro* potency correlates with *in vivo* immunogenicity."	Please clarify that once this correlation has been made, it is possible for potency to be assessed solely on the basis of the *in vitro* assay following licensure. Please clarify the following: the type of quantitative potency assays that can be used, in what (relevant) models, by what phase of development, and what correlations - surrogates related CMI responses in humans.
Section II B/Paragraph 2/ Line 3	"We recommend that you characterize the product for the extent of supercoiled plasmid in the bulk preparation and that you establish a minimum specification (preferably >80%)."	Please provide clarification for the suggested 80% supercoiled DNA figure. Sponsors may benefit from clarification for suitable limits and acceptance criteria material to be used in Phase 1 when only limited data from a small number of batches may be available. GSK suggests including wording that as development proceeds, suitable limits and acceptance criteria should be applied to demonstrate purity, quantity, identity, potency and safety (impurity profile) of each lot of pDNA.
Section II C/Paragraph 1/ Line 1 and Line 3-5	"We recommend that you test the final DNA vaccine product for potency, general safety..."	Plasmid DNA products, although not currently defined as well characterized, as per the FDA definition or ICH Q6B, are manufactured by rDNA technology using a well defined manufacturing process designed to remove/not introduce extraneous toxic contaminants. GSK suggests that FDA include text that it is possible to accept justifications to not perform this test based on characterization of the purity/impurity profile of each lot of drug substance/drug product.
Section III A/Paragraph 1/ Line 1	"Changes to the DNA sequence of the insert gene or vector sequences of a DNA vaccine would require the submission of a new IND..."	This suggests that a new IND would be required whatever the change. There may be some circumstances where it would be beneficial to file modified plasmids under the same IND e.g. plasmids that vary only in the HA encoding region for different flu strains (Note: new strains of egg based vaccines can be filed to an existing BLA). This scenario seemed possible under the 1996 guideline. Clarification on the requirements for a new IND is needed.
II B/Paragraph 2	"We advise you to establish the identity and amount of each plasmid component in the vaccine preparation to ensure lot to lot consistency"	Clarification is requested on the scenarios this section refers to and the level of characterization of the drug product that is expected for each scenario, e.g., dual plasmid product versus a "shotgun cloned" entire genome.